FC5: Growth and Syndromes

Phase 2 Trial of Vosoritide Use in Patients with Hypochondroplasia: Pharmacokinetic/ Pharmacodynamic Analysis from 12 Month Data

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DISCLOSURE STATEMENT

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I declare that I have no potential conflict of interest.

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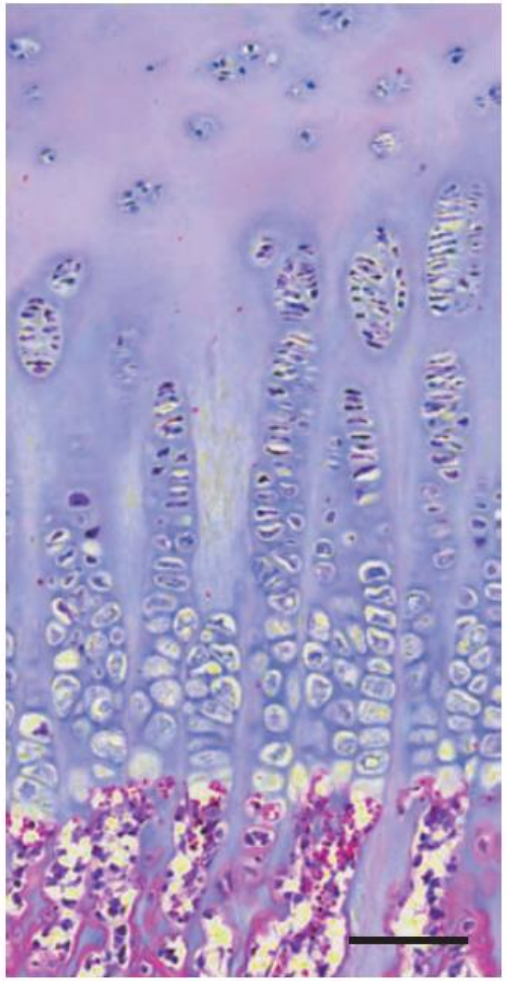
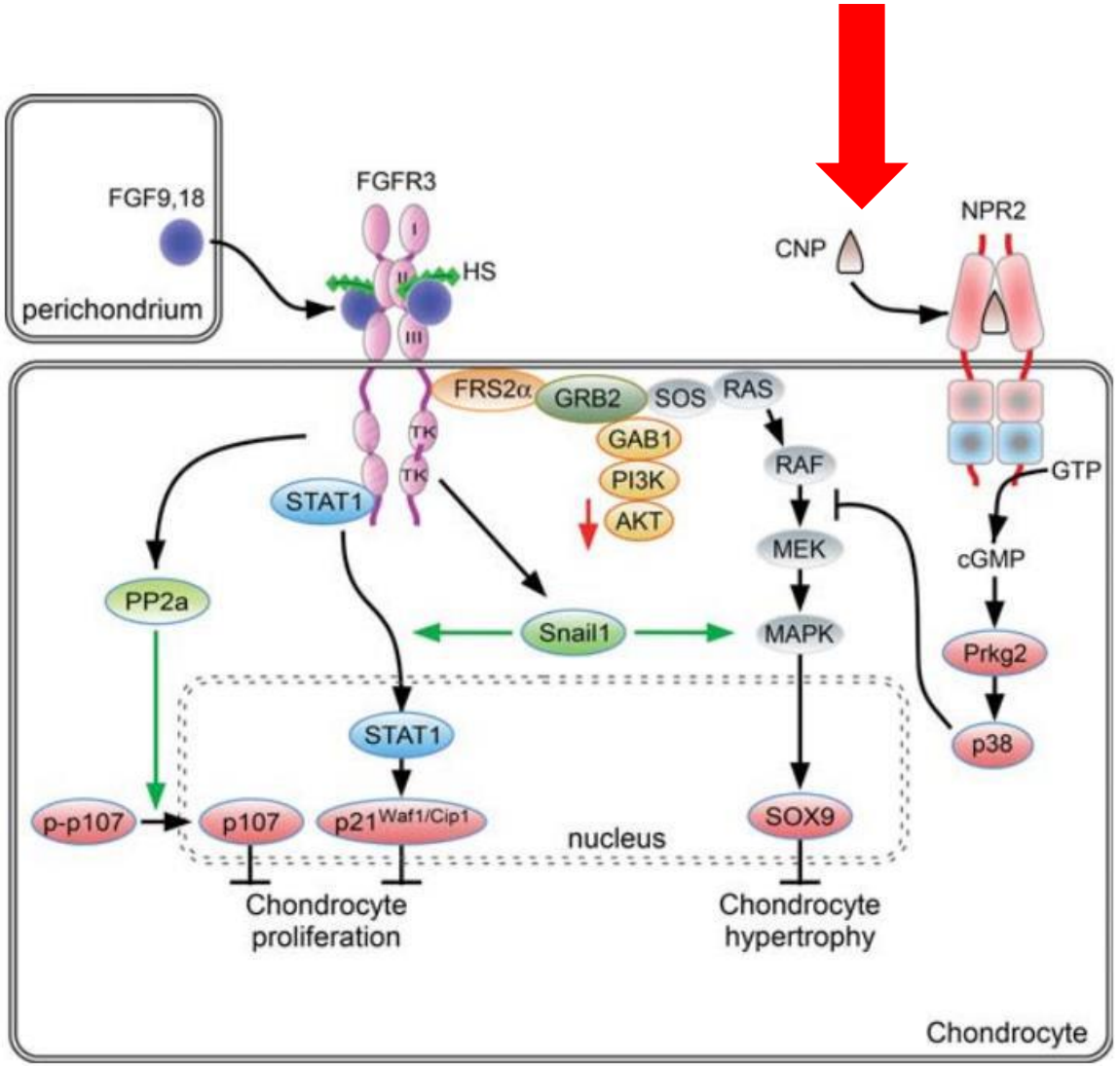
Hypochondroplasia Overview

- Autosomal dominant skeletal dysplasia
- Activating variants in *FGFR3*
  - p.Asn540Lys most common
- Prevalence estimated between 1 in 15,000-40,000
- Disproportionate short stature
- Mean adult height of ~131 cm for females and 144 cm for males[1]
- No approved therapies

1. Arenas et al. *Journal of Pediatric Endocrinology and Metabolism*. 2018;31(11):1279-1284.

What is vosoritide?



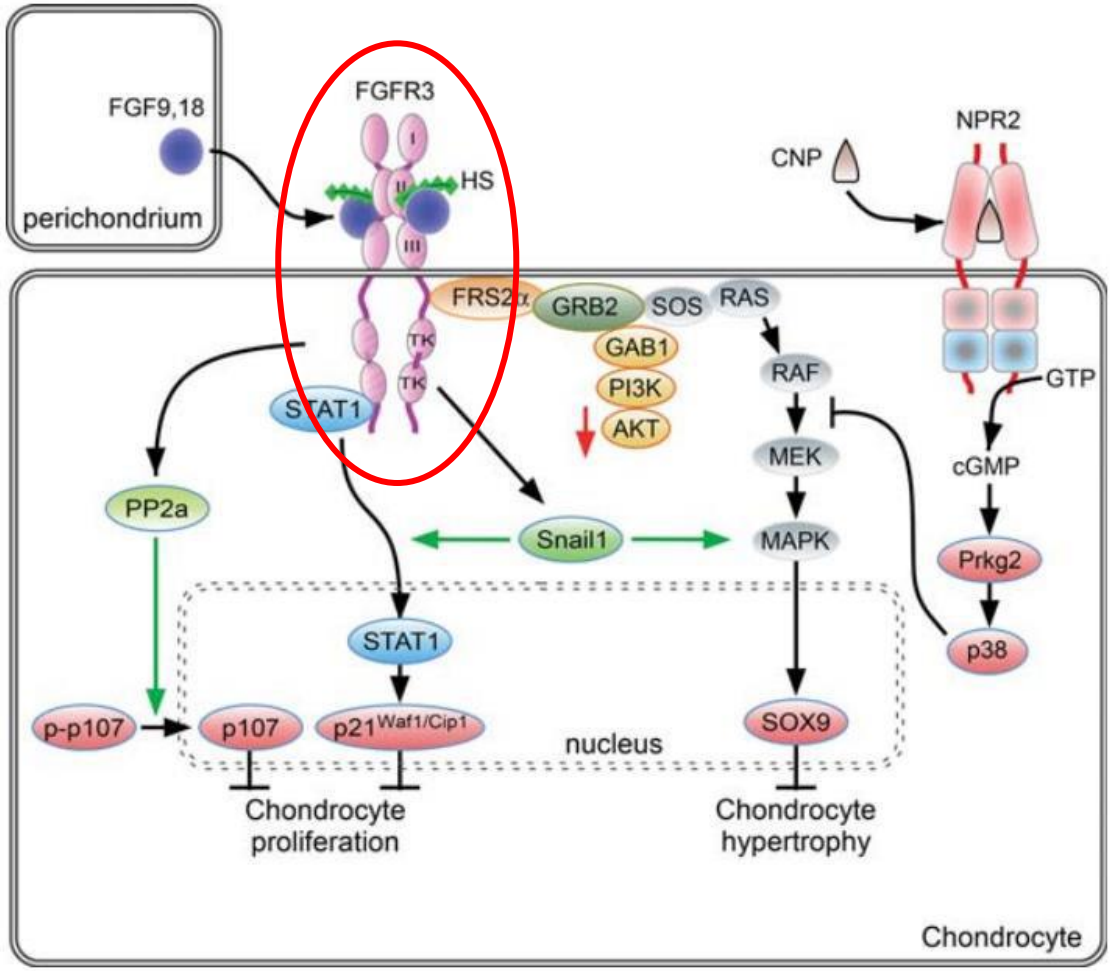


Baron J et al. Short and tall stature: a new paradigm emerges. Nature Reviews Endocrinology 2015;11(12)735-46.
Ornitz DM et al. Fibroblast Growth factor signaling in skeletal development and disease. Genes Dev. 2015;29(14):1463-1486.

Vosoritide for Selected Genetic Causes of Short Stature

- Hypochondroplasia

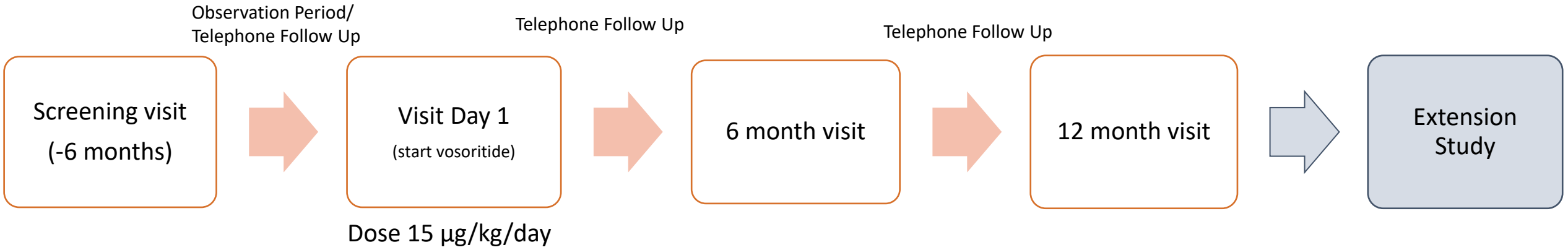
- CNP Deficiency
- Heterozygous NPR2 mutation
- RASopathy (Noonan Syndrome)
- SHOX Deficiency
- Aggrecan Deficiency



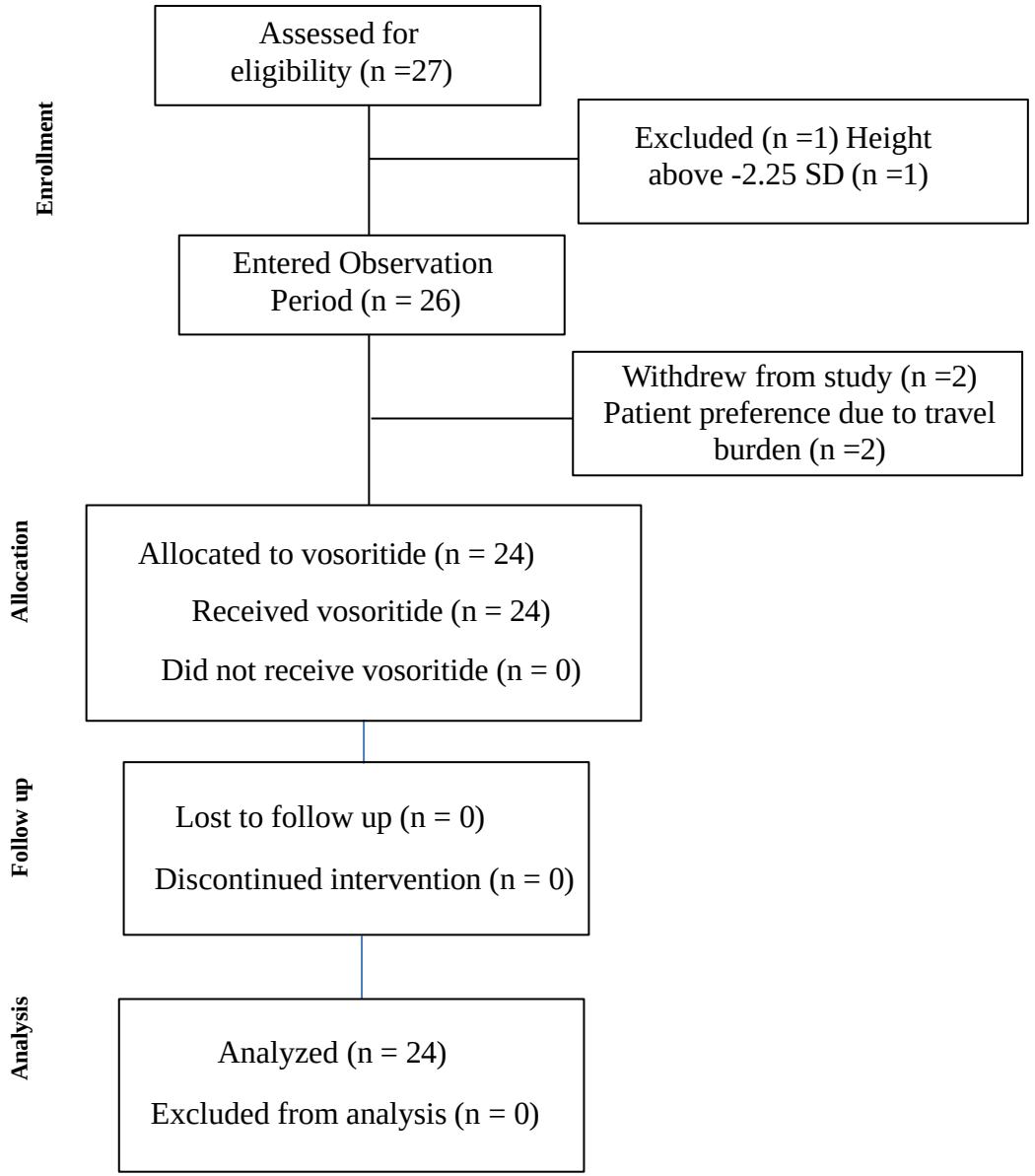
Ornitz DM et al. Fibroblast Growth factor signaling in skeletal development and disease. Genes Dev. 2015;29(14):1463-1486.

Inclusion Criteria and Study Design

- Age >3 years 0 days AND <10 years 364 days for males, <9 years 364 days for females
- Pre-pubertal
- Patient height <-2.25 SDS
- Variants in one of the 6 categories
- Absence of growth hormone deficiency
- No concurrent treatment with GH (prior treatment is OK).
- No other significant medical history
- No hypertrophic cardiomyopathy



Hypochondroplasia subjects only:

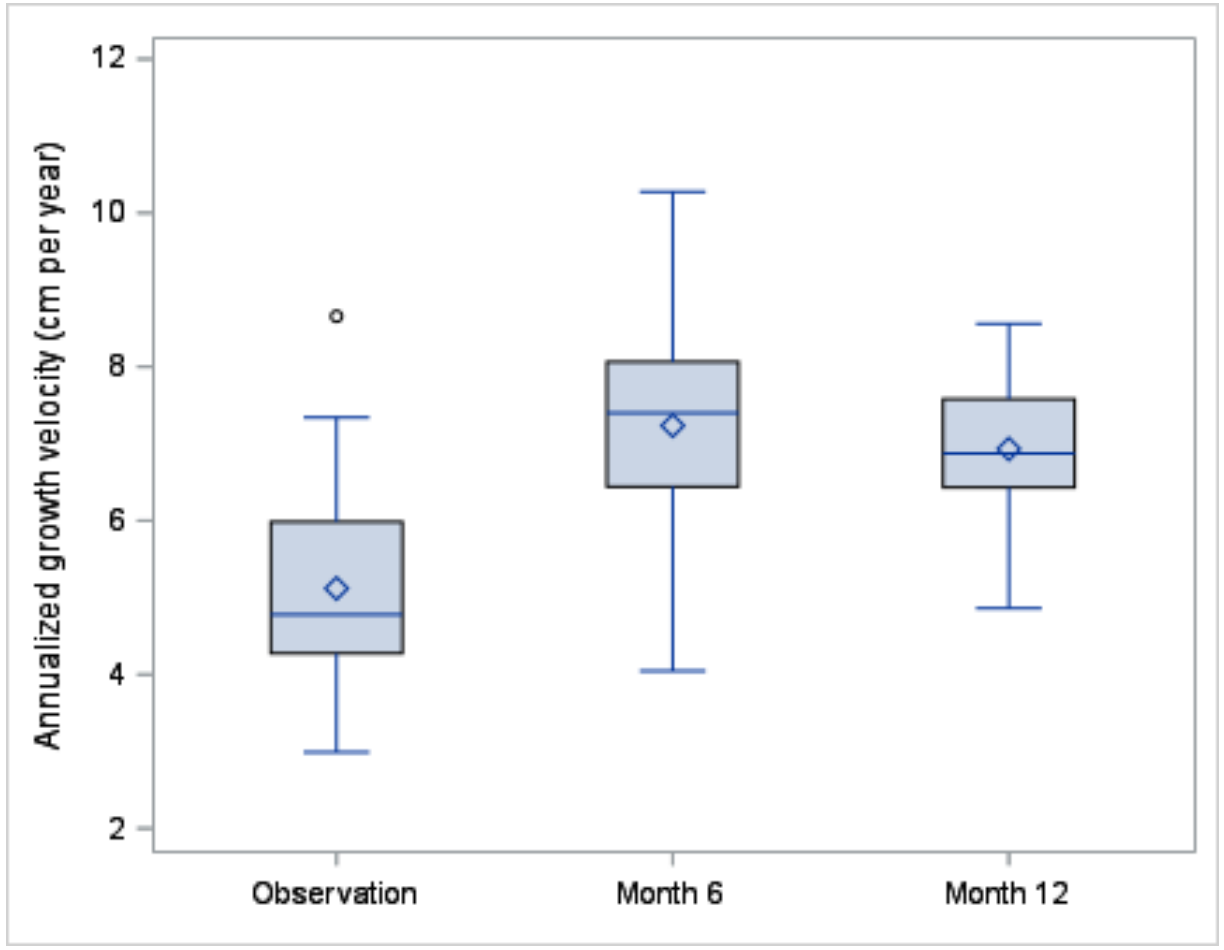


Dauber et al. eClinicalMedicine 2024.

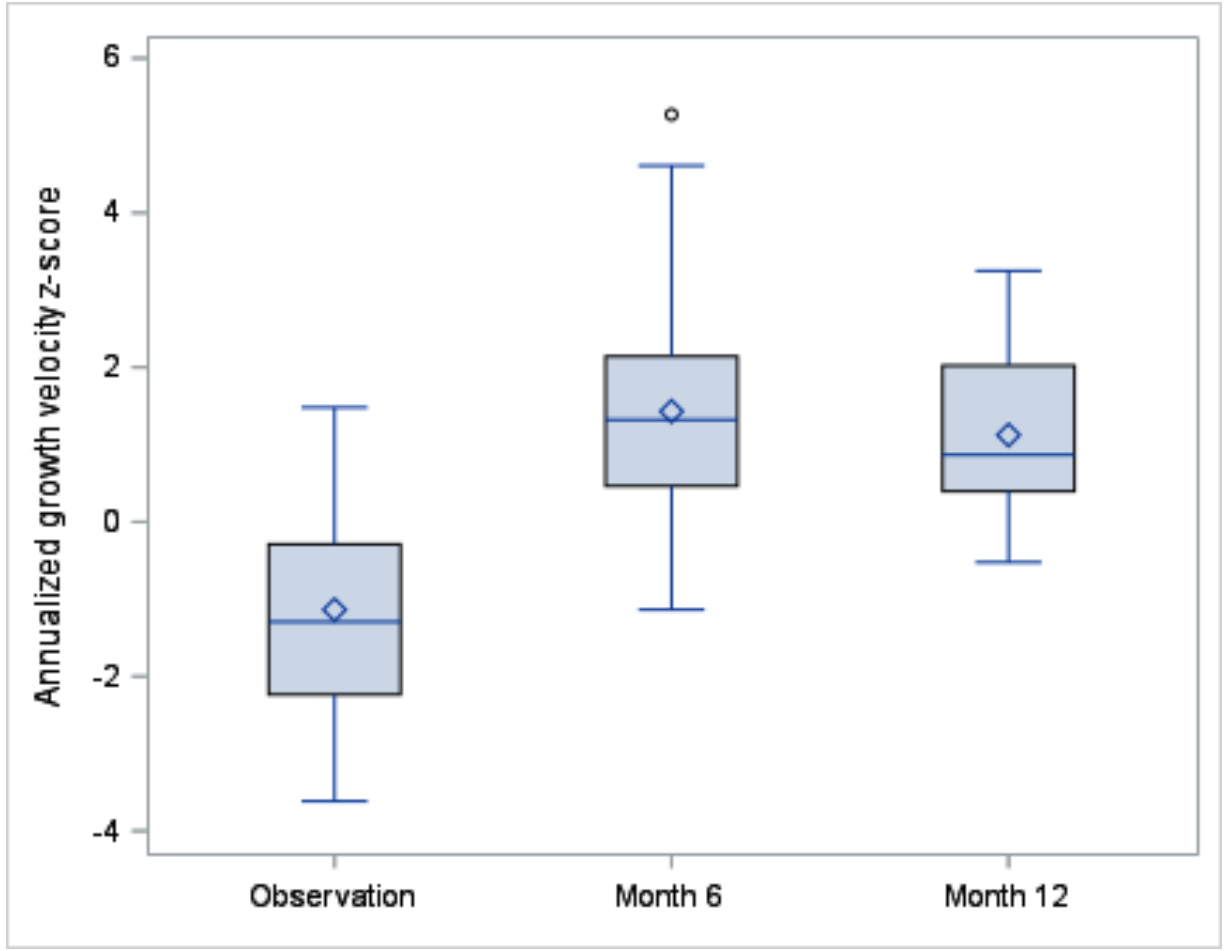
Total enrolled subjects	N=24
Age at screening (years) mean (SD); median (IQR)	5.86 (2.29); 5.55 (2.39)
Age group # (%)	
3 to <5 year	10 (41.7%)
5 to <9 year	11 (45.8%)
9 to <11 year	3 (12.5%)
Sex	
Female	12 (50%)
Male	12 (50%)
Race	
Caucasian	17 (70.8%)
Asian	4 (16.7%)
Other	3 (12.5%)
Ethnicity	
non-Hispanic/Latino	23 (95.8%)
Hispanic/Latino	1 (4.2%)
Previously treated with growth hormone	
Yes	3 (12.5%)
No	21 (87.5%)
Genetic Variant	
Asn540Lys	22 (91.7%)
Gly342Cys	1 (4.2%)
Ser351Phe	1 (4.2%)

Hypochondroplasia- Height Velocity Outcomes

Annualized Height Velocity



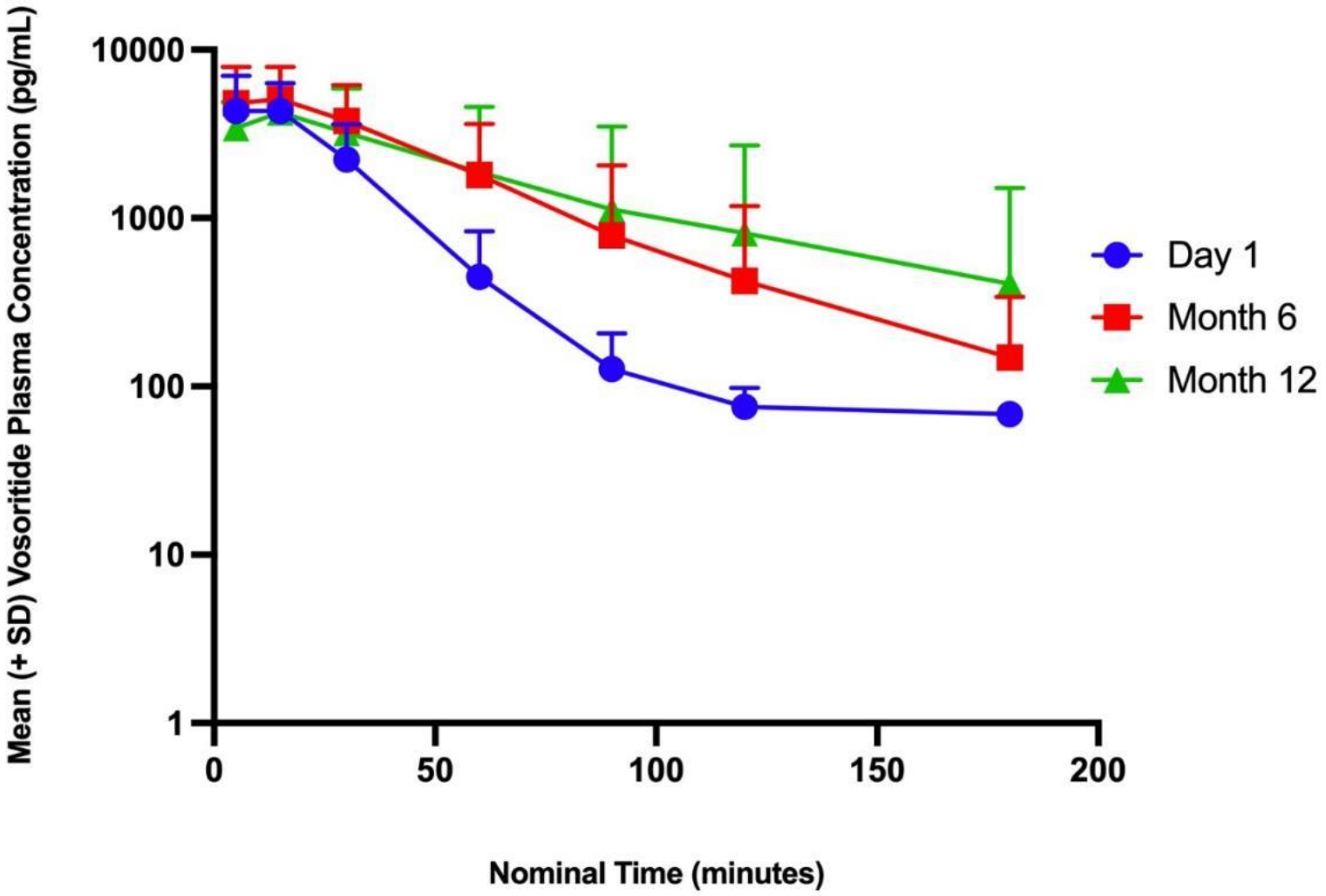
Annualized Height Velocity Z-score



1.81 cm/year increase in AGV; 2.26 SD increase in AGV Z-score

Dauber et al. eClinicalMedicine 2024.

Pharmacokinetics (PK):

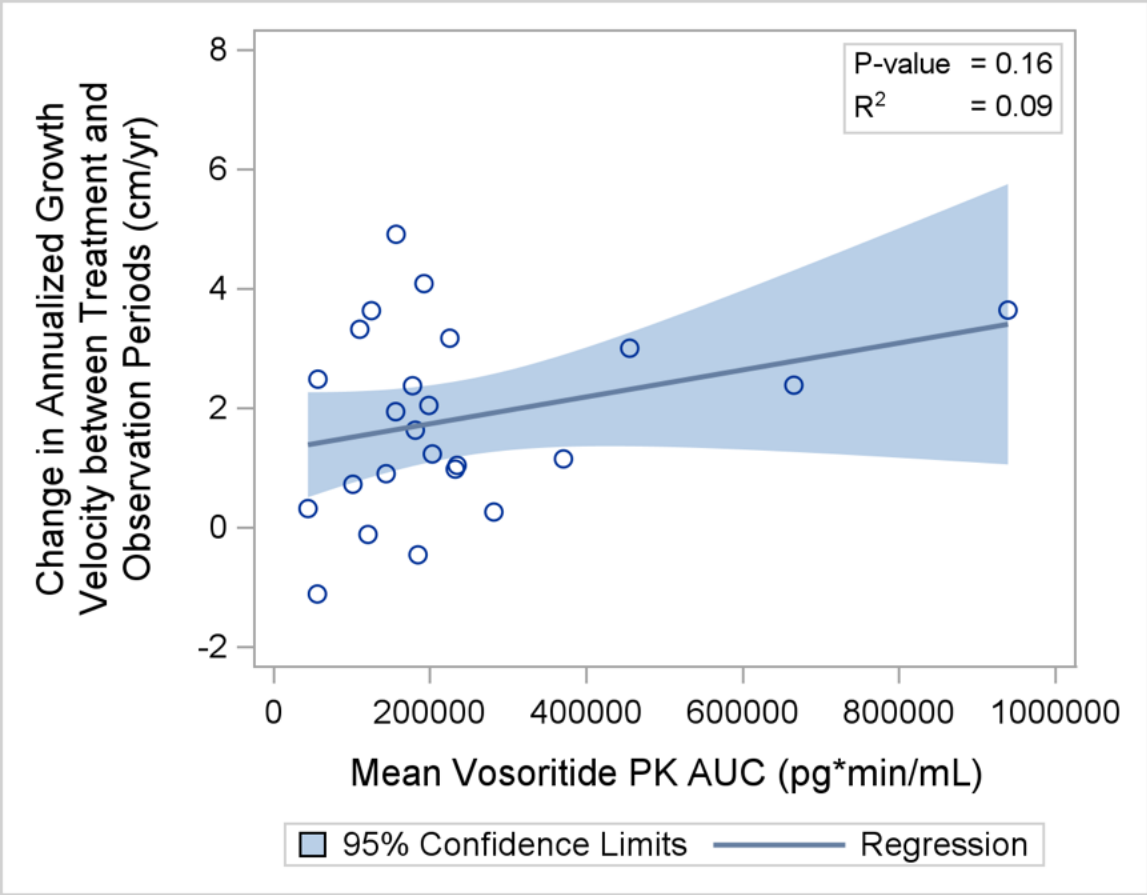


- Median T_{max} = 14 minutes
- Median $T_{1/2}$ = 20.6 minutes
- Mean apparent clearance (CL/F) = 95.2 mL/min/kg
- Mean apparent volume of distribution (V_z/F) = 2910 mL/kg

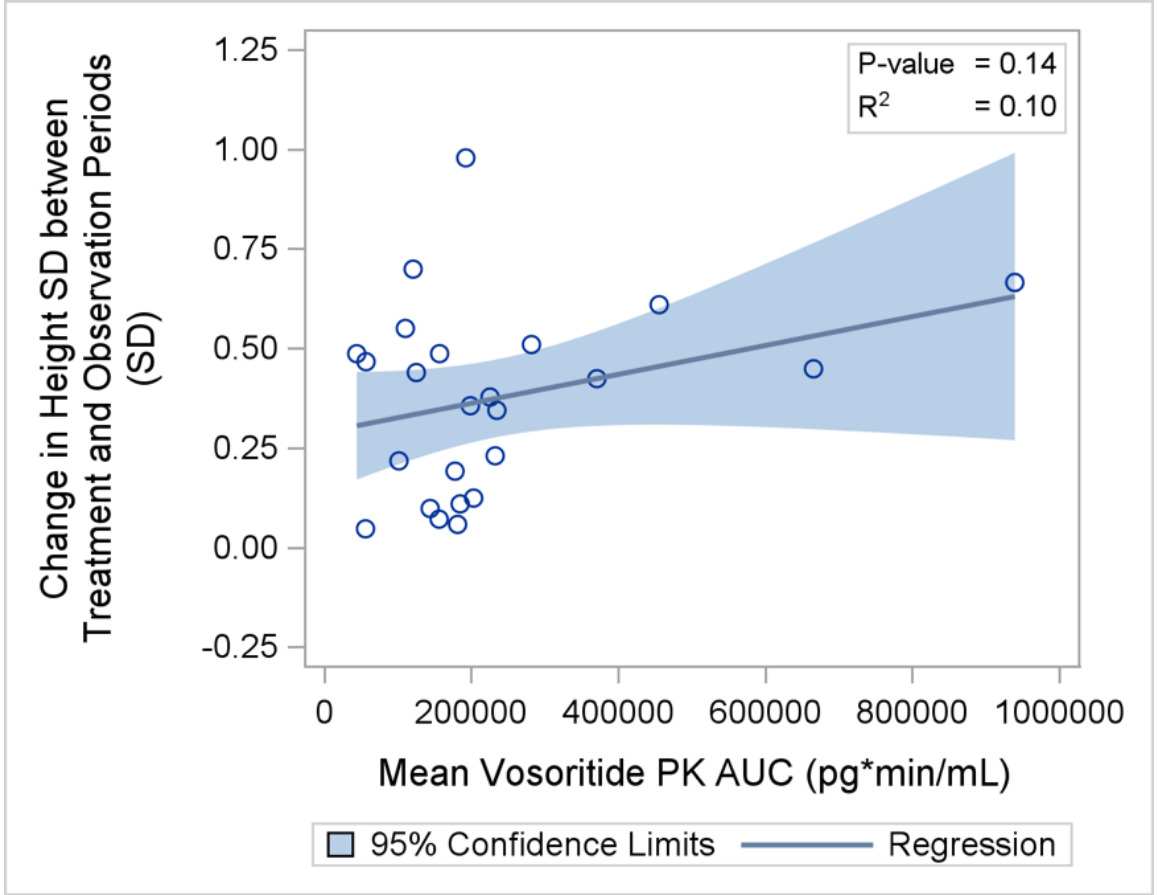
- Similar to what has been reported for achondroplasia

PK in relation to clinical outcomes:

Change in Annualized height velocity (AHV)

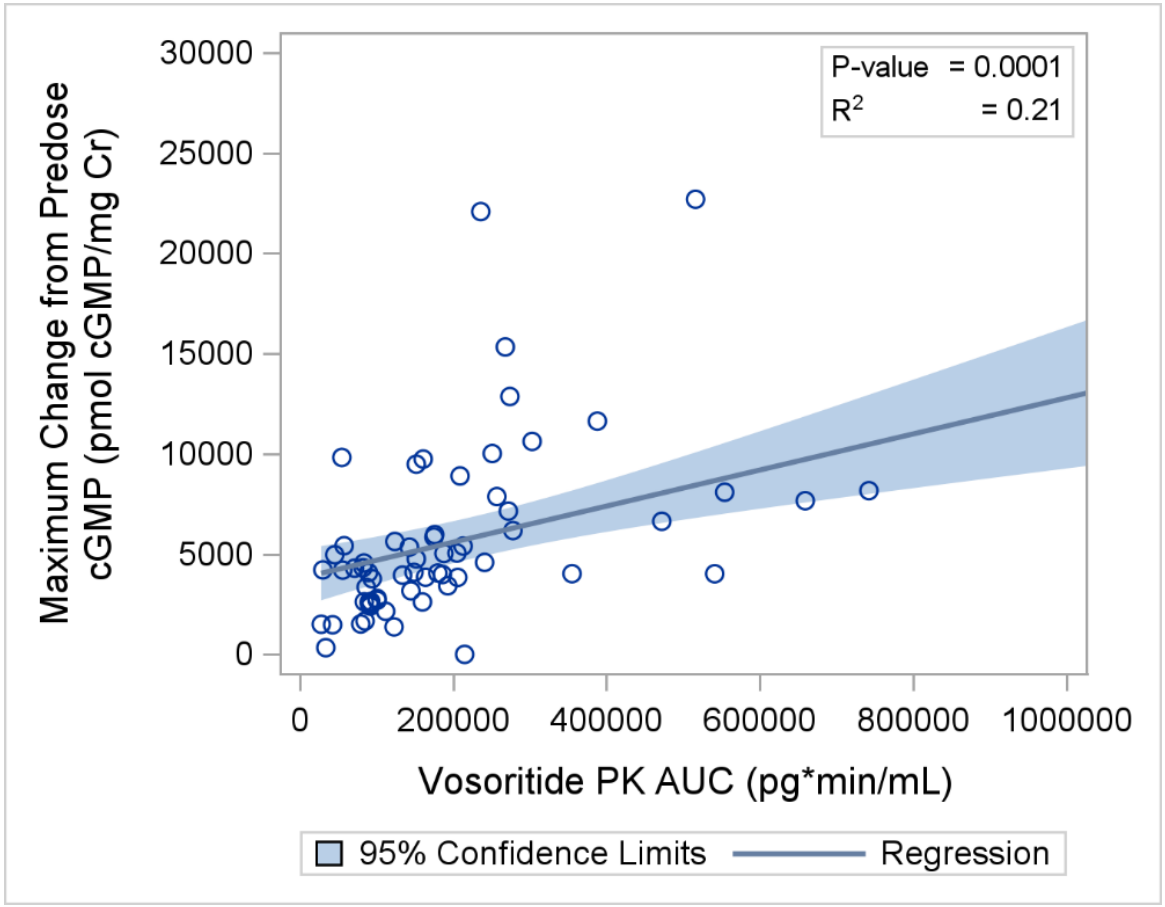


Change in height SD

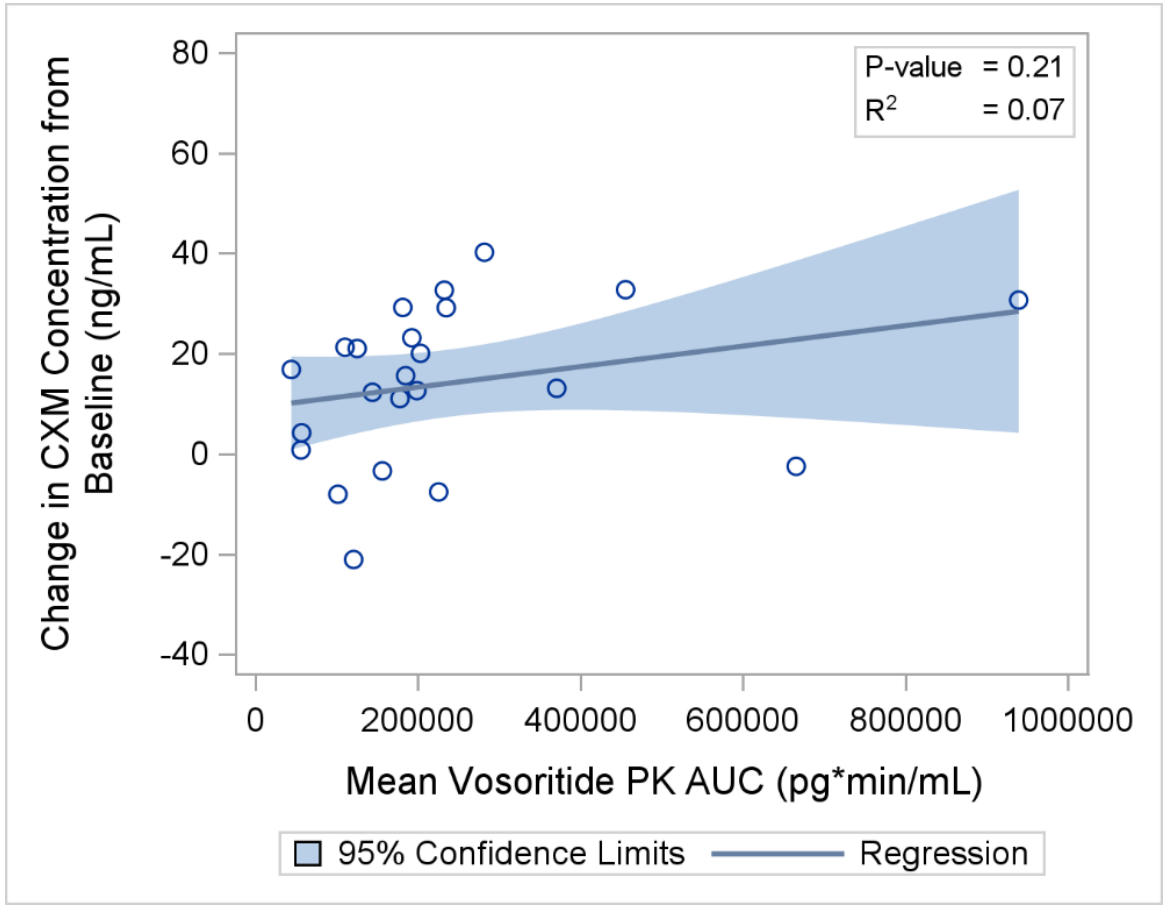


PK and Biomarkers: uCGMP and CXM

Maximum change in cGMP

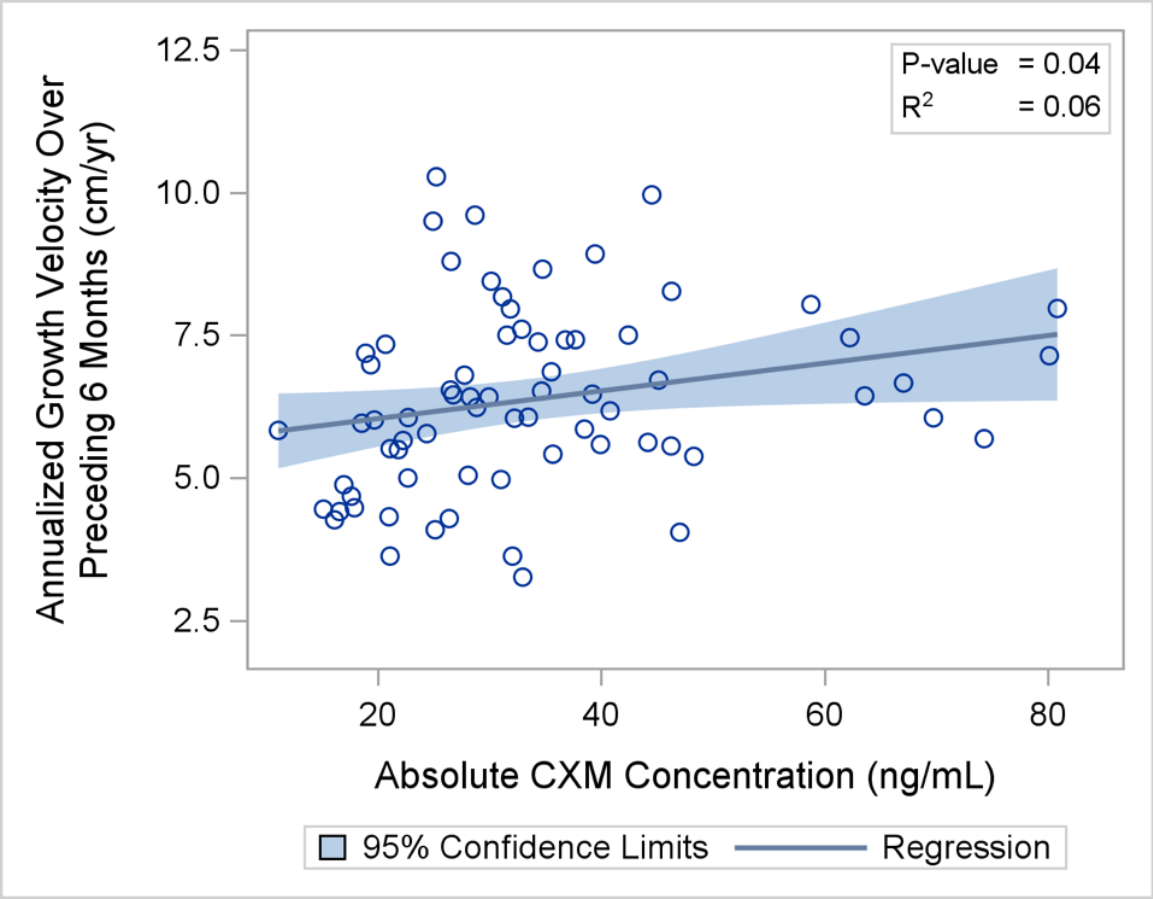


Change in Collagen X Marker (CXM)

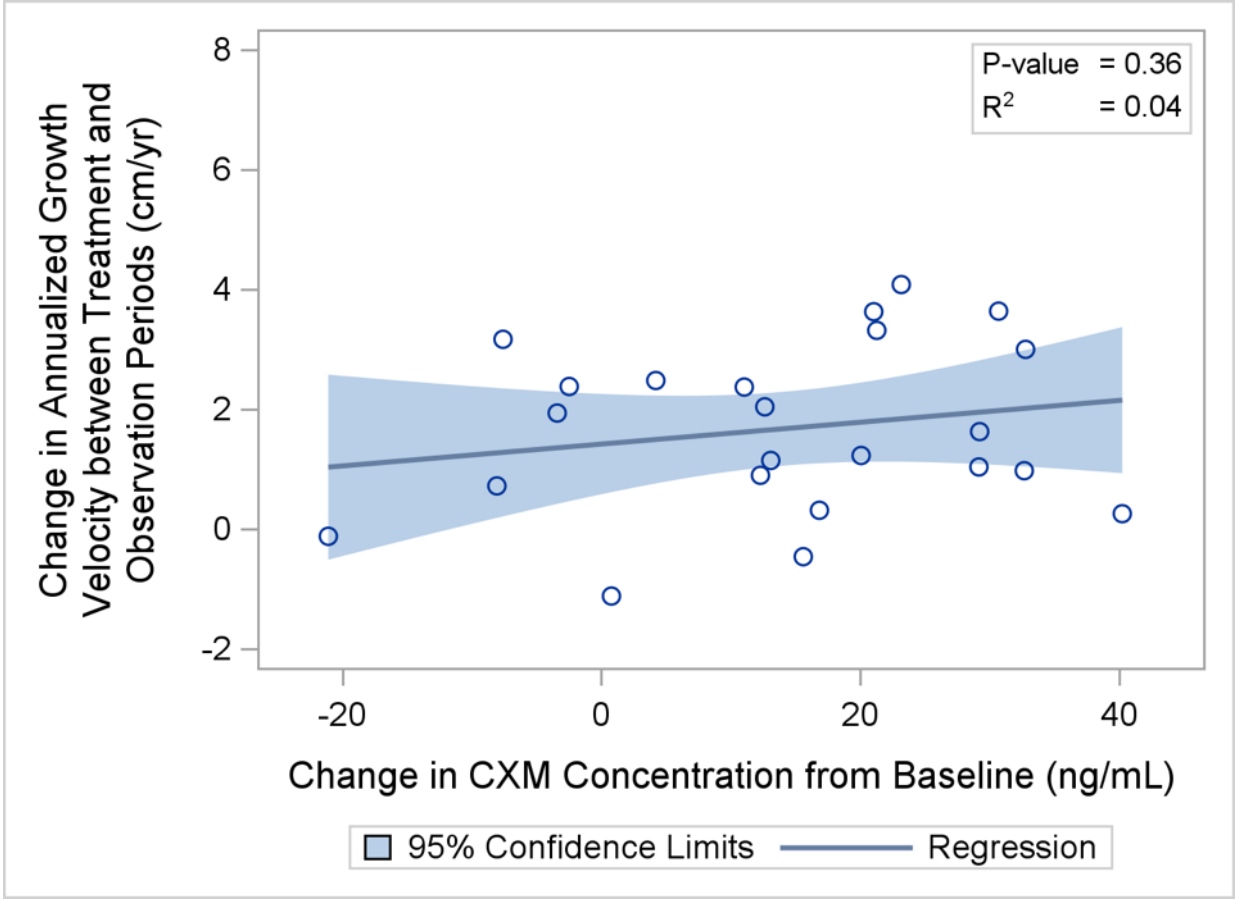


Biomarkers and Clinical Outcomes:

AHV over CXM



Change in AHV over Change in CXM



Conclusions

- Vosoritide treatment showed improvement in AHV and height SD in children with hypochondroplasia.
- Vosoritide PK was similar to previously reported in children with achondroplasia supporting a similar dosing regimen.
- There were no strong correlations between PK or PD parameters and growth outcomes.
- Additional research is needed to identify factors which could help predict response to vosoritide in children with hypochondroplasia.

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THANK YOU

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